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By V. A. Kovanev

N. F. Mistakopulo et al

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ON CERTAIN PROPERTIES OF MUSCLE RELAXANTS

Following is the translation of an article by V. A. Kovanev, N. F. Mistakopulo, G. A. Ryabov, and V. P. Smol'nikov entitled "O Nekotorykh Svoystvakh Myshechnykh Relaksantov" (English version above) in Vestnik khirurgii imeni I. I. Grekova (Herald of Surgery imeni I. I. Grekova) Vol. LXXXIV, No. 5, 1960, pages 77-81.

From the Laboratory of Anesthesiology (Head -- Candidate of Medical Sciences V. P. Smol'nikov) of the Institute of Thoracic Surgery (Director -- Professor A. A. Busalov) of the Academy of Medical Sciences USSR.

An important place in the large arsenal of anesthetic agents belongs to the relaxants, the use of which permits one to diminish the quantity of narcotic substance necessary for the operation, to conduct surface narcosis and controlled respiration. Modern anesthesiology is unthinkable without the use of relaxants, and now the moment has come when the necessity has arisen not only of collecting the quantities of operations which have been conducted with relaxants, but also of the deepened study of their properties which are manifested at the time of the operation and postoperative period, the peculiarities of their interaction with other pharmacological substances and with each other.

In the present communication we are not trying to give exhaustive information concerning the properties of the muscle relaxants; at the same time it seemed expedient to us to indicate certain of their properties, which are maximally important in clinical practice, which have been successfully detected as a result of the use of relaxants for more than 1,000 patients who had been operated on.

There are numerous communications in the literature concerning the clinical properties of succinylcholine (ditilin). To this we consider it necessary to add the results of our observations concerning the length of action of this relaxant at the time of operation. According to the opinion of the Danish authors (Polzen, 1952; Ibsen, 1953;

Mohelsky and Ruben, 1953; Kristiansen and Jensen, 1954), succinylcholine possesses the property of tachyphylaxia i. e., a shortening of the length of the curarizing effect in the presence of every successive administration of the relaxant. Our observations on 70 narcoses in the presence of digital commissurotomy, conducted by the fractional method of administering succinylcholine (in a dose of 100 mg in the presence of the first signs of the restoration of the muscle tonus), have shown, that tachyphylaxia took place in one case, regular intervals between the administrations of the succinylcholine relaxant -- in 16 cases, and a lengthening of the action of succinylcholine was observed in 53 cases. This lengthening begins from the second half of the operation and most often from the moment of cardiac manipulation (32 cases). It is well known that succinylcholine (ditilin) is rapidly hydrolyzed by pseudo cholinesterase into choline and succinic acid. The investigations of Foldes (1957) have shown that succinylcholine is also cleaved in an alkaline medium. However, the entire hydrolysis proceeds in two steps: 1) a rapid decomposition into choline and into succinylmonocholine; 2) a decomposition of the latter, in its turn, into choline and succinic acid.

The intermediate product -- succinylmonocholine -- also possesses the properties of a relaxant, but is slowly subjected to decomposition by pseudocholinesterase and is destroyed chiefly by alkaline hydrolysis or is excreted from the organism by the kidneys. At the time of operative intervention under conditions of narcosis a depression of the excretory capacity of the kidneys occurs (A. L. Petrov, 1954), and a lowering of the blood pressure at the time of commissurotomy and after it still more depresses the function of the kidneys. These data provide a basis for assuming that in the presence of the repeated administration of the relaxant, a definite quantity of succinylcholine is accumulated in the organism of the patient, due to which the relaxation of the muscles is lengthened. The conception advanced concerning the significance of the lowering of the arterial pressure for lengthening the action of the succinylcholine has also been confirmed by observations conducted with the use of arfonad, in which in the intervals between the administrations of the relaxant, the apnea was more prolonged from those same doses, than without arfonad. Thus, one can consider that in the presence of successive administrations of succinylcholine, its action is lengthened due to the accumulation of an intermediate product and depends on the alkaline medium of the organism, the function of the kidneys, and the arterial pressure. We have also observed the property of succinylcholine which has been detected in

the presence of other operations (congenital heart defects, operations on organs of the abdominal cavity) and have also noted a lengthening of the action of relaxants in the presence of repeated administrations.

The property of succinylcholine which has been considered is not constant or always sufficient, and the lengthening can set in at various stages of the operation. On the other hand, in a number of cases the necessity arises of obtaining a more prolonged relaxation of the muscles at important stages of the operation, retaining at the same time all the positive properties of relaxants of the depolarizing type. In experiments on animals A. F. Danilov and S. R. Rybolovlev (1957) have shown that the intravenous administration of proserine lengthens the action of succinylcholine. This is occasioned by the depression of pseudocholinesterase by the proserine. However under clinical conditions the results of these experiments have not been verified. Our experiments, conducted on animals, have confirmed the literature data and have shown that with the aid of proserine one can achieve an average lengthening of the action of succinylcholine of 47 minutes. This method has also given positive results under clinical conditions. In 23 different operations the duration of the apnea fluctuated from 60 to 120 minutes (on the average -- around 80 m) and was increased via the administration of atropine (for removing the bradycardia), proserine, and the subsequent administration of succinylcholine at definite intervals (10 minutes). These observations have shown that the longer the interval between the administration of proserine and of succinylcholine, the more pronounced was the prolongation effect. This permits one readily to control the prolongation of the action of succinylcholine. When necessary we achieved the termination of the relaxation via the administration of adrenalin or the intravenous administration of 20-30 ml of blood.

From the theoretical point of view the combined use of succinylcholine with proserine does not appear to be justified, since proserine under these conditions considerably distorts a multiplicity of functions of the organism and thus converts the local process of curarization into a general process with a wide range of changes in the organism; however, taking into account all the negative properties of the proposed method, we turn our attention to the circumstance that in the presence of other forms of curarization there also takes place a utilization of proserine which in any case can be considered as undesirable. Nevertheless, the possibility of avoiding the danger of restoration of the muscle tonus in the crucial moments of the operation, and also the possibility of diminishing the total quantity of relaxant,

as it seems to us, to a considerable extent compensates for this shortcoming. In our own practice we have not observed any complications associated with the use of this method.

In rare cases for causes which are still unknown to us a lengthening of the action of the relaxant of the depolarizing type can be observed which can be considered as a pathological state. We have in view the so-called pseudocholinesterasopenia and cases of "double block". We have already stated that succinylcholine (ditilin) is hydrolyzed by the pseudocholinesterase which is found in the plasma and is cleaved in an alkaline medium. In rare cases the plasma contains very little pseudocholinesterase, and in such individuals the hydrolysis of succinylcholine proceeds extremely slowly. We have observed apnea in one patient which lasted one hour 20 minutes after the administration of 75 mg of succinylcholine. The treatment of the apnea evoked by pseudocholinesterasopenia, consists in the transfusion of blood, since it is assumed that the blood of the donor will contain a normal quantity of pseudocholinesterase. In our case the respiration was restored after the administration of 500 ml of blood.

By so-called "double block" is implied a state of prolonged paralysis of the muscles and apnea, evoked by the administration of a relaxant of the depolarizing type, which then for still unknown causes is converted into paralysis and apnea of the nondepolarizing type. In one of our cases, after the third administration of curacite /kuratsit/ in a quantity of 60 mg apnea ensued which lasted for two hours. We initially thought that we were dealing with pseudocholinesterasopenia, although it was difficult to explain the fact that in the patient hydrolysis of the preceding doses of succinylcholine proceeded in normal periods. After an hour of the apneic state we began transfusion of blood and transfused 500 ml intravenously without any signs of restoration of the muscular tonus. After the transfusion of blood had proved to be without results, we decided that we were dealing with "double block". The administration of 0.5 mg of atropine and 0.25 mg of proserine intravenously rapidly restored the respiration, and the patient /female/ woke up.

The anesthesiologist must always have the possibility of such a complication in view and must know that its treatment consists in the administration of proserine. However, if apnea of the depolarizing type develops, then the administration of proserine alone deepens the apneic state and prolongs it. Consequently it is more rational to use not proserine, but tensilone, which possesses an anticholinesterase action, as does proserine also, but one which is briefer.

The described case is also interesting on account of the fact that in the patient the respiration was twice restored after succinylcholine, i. e., paralysis of the diaphragm of the depolarizing type occurred twice in her, and after the third dose paralysis of the nondepolarizing type ensued.

Thus, in the absence of antagonists (proserine, tensilone), it is undesirable to use depolarizing relaxants, and also competitive relaxants. In the case of the onset of a prolonged apnea and in the presence of blood transfusion which is without results, the sole thing which the anesthesiologist can do is to continue artificial respiration in the hope that the organism after this time will cope with the excess of relaxants.

It is necessary to note that such a complication as "double block" is encountered very rarely and should be diagnosed with extreme care, since an erroneous diagnosis will be associated with the erroneous use of proserine which still more deepens and lengthens the paralysis of the muscles and complicates the situation extremely.

In many clinics a method of muscle relaxation is used up to the present time which consists in this that relaxants of two different types, possessing a different mechanism of action, are simultaneously introduced into the patient's blood. As a rule, succinylcholine (ditilin) is initially administered and immediately after this, diaplacin. The curarization induced by one of these relaxants, ordinarily proceeds in strict sequence. The muscles of the face and head are paralyzed first, then the extremities, the intracostal muscles, and finally, the diaphragm, are immobilized. When the action of the relaxant is terminated, the muscular tonus is restored in the reverse order.

When two different relaxants are simultaneously administered, a completely different picture is often observed. It initially seems that the patient in general does not sleep. He waves his arms, bites the intubation tube, turns on his side, opens the eyes. An impression of some sort of muscular anarchy is created; however, a more intent observation of the patient convinces one that the anarchy is only apparent. The muscle relaxation here also has its patterns. At the same time that the muscles of the face and extremities are completely active, all the muscles of respiration or, at least, of the diaphragm, are paralyzed. We had the possibility of observing in our practice a similar syndrome and have called it the "inversion of the symptomatology of curarization". The existence of an antagonism between relaxants of the depolarizing and nondepolarizing types of action is well known from the works of foreign authors. French authors have writ-

ten of "dissociation", without going into the details of this dissociation. Americans have advised that two relaxants not be administered together. However, practice sometimes requires the use of both relaxants in the course of narcosis. We have noted that an interval between the administration of succinylcholine and diplacin, equal to 20 minutes, prevents the development of inversion. Inversion is dangerous not in itself, but because it imitates the insufficiency of the dosage of the relaxant and impels the inexperienced anesthesiologist to the use of unjustifiably high doses of diplacin. This, in its turn, leads to the administration of large doses of proserine in the postoperative period, which is also fraught with menacing complications.

As our experiments and clinical observations have shown, one can succeed in removing the developing inversion of the symptomatology with proserine in the beginning of its development, which then permits one calmly to pass on to an average dose of diplacin.

When relaxants of the nondepolarizing type are used, such a complication as recurarization is possible, in which after some time in the patients with restored muscle tonus there anew develops paralysis of the voluntary musculature in the same sequence as is observed in the presence of curarization.

The first case of recurarization which arose after the use of flaxedil, was described by Fairley in 1950. Montgomery and Bennett-Jones have subsequently written concerning this (1956).

We have observed seven cases of recurarization, which were terminated satisfactorily. We present one observation.

Patient Female S., 30 years in age, was operated on in August 1957 on account of mitral stenosis. Introductory narcosis with penpentothal. Intubation after the administration of curacite (ditilin). Narcosis with nitrous oxide with oxygen in a ratio of 3:2 with the use of a relaxant (an analogue of the Soviet pyrolaxon); the patient received in all 240 mg of the relaxant. At the end of the operation the respiration was completely restored by the administration of 0.5 mg of atropine and 2 mg of proserine intravenously. The consciousness returned on the operation table. In the postoperative ward the patient answered question, moved her arms. After two hours obliteration of the speech appeared, the patient lay with closed eyes, raised the eyelids with difficulty, the arms were flexed at the elbows with great difficulty, the shoulder muscles were completely paralyzed. The respiration was slightly hampered, she could not bend the legs at the knees. Recurarization was diagnosed,

0.5 mg of atropine and 0.5 mg of proserine were administered intravenously. After 5 minutes all the phenomena of paresis disappeared, the patient opened her eyes, put the hands on her head, her speech became articulate and clear. The post-operative period proceeded smoothly.

The first observations forced us to undertake certain organizational measures. A continuous observation by the anesthesiologist of the patients was established for the course of the first two to three hours after the operation. Proserine and atropine were introduced into the kit for emergency aid.

Recurarization is particularly dangerous in the night in the half-dark ward, when the patient is not in a state to cry out and press the button of the bell. Death ensues under these conditions from asphyxia. The accumulation of carbon dioxide leads to edema of the brain. As the work of Fairley and our observations have shown, recurarization does not set in suddenly.

In our first observation two hours passed before the first symptoms appeared, in other cases, tens of minutes passed. We would like to express the hypothesis, that in the presence of the attentive observation of the patient one can diagnose the onset of recurarization long before the development of apnea. We also assume, that in the presence of the ascertaining of a depression of respiration, it is not necessary to reintubate the patient; it is quite sufficient to administer proserine intravenously and to wait several minutes. It is very possible that recurarization is encountered much more often than it is diagnosed. There are obliterated forms, where inadequate respiration in the post-operative period is ascribed to pain, particularly in the presence of operations on the thorax.

Conclusions

1. We were able to convince ourselves experimentally and clinically that the length of the action of succinylcholine can be increased with the aid of proserine to the desired periods.

2. The anesthesiologist in his practice can encounter such complications as "double block," for the treatment of which proserine should be used, provided only that one is absolutely convinced of the correctness of the diagnosis.

3. The simultaneous use of relaxants of different types of action is undesirable, since it can be complicated by an inversion of the symptomatology of curarization which hampers the orientation of the anesthesiologist with respect

to the clinical picture and can lead to the use of dangerous doses of the relaxant and of proserine.

4. The use of relaxants of the nondepolarizing type is rather frequently complicated by recurarization which is particularly dangerous in the absence of constant observation of the patients.

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